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1 Guidelines for Primary Aldosteronism: Uptake by Primary Care Physicians in Europe.

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Abstract

Context: Primary aldosteronism (PA) is the most frequent form of secondary hypertension but is still markedly underdiagnosed. In 2008 the Endocrine Society released guidelines for PA diagnosis and management; current indications are that they are not being widely followed. **Objective:** To investigate the level of knowledge and application of the guidelines in a large representative cohort of general practitioners (GPs) in Italy and Germany. **Setting and Design:** The study was carried out by web questionnaire on hypertension and PA management with 500 GPs (250 in Italy and 250 in Germany), stratified by geographical area and city size. **Results:** The mean number of patients seen was 1747 (Germany) and 1388 (Italy). Of these, 18% were diagnosed as hypertensive in Italy and 25% in Germany. Renin and aldosterone measurements were ordered by 7% of GPs in Italy and 8% in Germany. GPs in Italy considered 8% of patients eligible for aldosterone and renin measurements compared to 13% of GPs in Germany. In Italy, PA prevalence was 1% among hypertensive patients; 36% of the GPs reported no PA patients under their care or diagnosed previously. In Germany, the prevalence of PA was 2% among hypertensive patients; 19% of GPs had no PA patients. **Conclusions:** in Germany and in Italy, PA is not widely recognized by GPs; Endocrine Society guidelines for PA diagnosis are not well known or applied, resulting in marked underdiagnosis of the disease.

Introduction

In 2008 the Endocrine Society published guidelines for the case detection, diagnosis and treatment of primary aldosteronism (1), co-sponsored by the European Society of Endocrinology. These guidelines recommended screening for primary aldosteronism in the ~30% of patients with a substantial risk of PA. Hypertension per se is a major driver of cardiovascular morbidity and mortality; the diagnosis of PA is of particular importance given the markedly higher risk profile than that in age-, sex-, and blood pressure-matched essential hypertension (2,3). The guidelines published by the Japan Endocrine Society in 2011 recommend screening all hypertensive patients for PA (4); in the revised guidelines recently published by the Endocrine Society in 2016 (5) the previous recommendation has been expanded to ~50% of hypertensives.

While such recommendations can be justified in theory, it is difficult to see how in the foreseeable future they might be put into practice. In developed countries it is estimated that 20-40% of the adult population have high blood pressure (BP). The estimated prevalence of PA currently varies from ~5% of hypertensives to >10%, a range reflecting strict or more relaxed cut-offs for plasma aldosterone concentration (PAC), plasma renin activity/concentration (PRA/PRC) and the aldosterone to renin ratio (ARR). If we take a figure of 30% for the prevalence of adult hypertension, this gives us ~ 70 million hypertensives in the USA, ~30 million in Japan, and ~15 million in Italy. Merely to tread water would require 4 million hypertensives to be screened each year in the US, 2 million in Japan and 1 million in Italy.

There is a general consensus that screening rates are in fact very much lower, and the 2016 guidelines are accompanied by a desk reference module for primary care physicians in an attempt to increase screening of patients at high risk of PA. The present study was undertaken to establish the extent to which primary care physicians (also known as general practitioners) are aware of the guidelines, and secondly their familiarity with the

management of primary aldosteronism. The study took place in Italy and Germany; in both these countries there are outstanding academic and clinical contributors to the fields of PA. There is much in common between the two countries' responses, and some differences. What it shows, in brief, is a yawning gap between theory, as laid down in guidelines, and practice. It is likely that a similar gap exists throughout the world.

Materials and Methods

The study was directed by the Department of Medical Sciences at the University of Turin, approved by the University's Institutional Review Board and supported by an untied grant from Diasorin s.p.a. The questionnaire was posed to 250 physicians in Italy and 250 in Germany by the market research firm Stethos srl using the CAWI (Computer Assisted Web Interviewing) methodology. All web interviews were collected between November 2013 and January 2014. The physicians chosen cared for at least one thousand monitored patients, and were stratified on the basis of practice location (village/small town/large town etc.) and geographical area (e.g. North, Centre, South of Italy, plus East and West for Germany). The questionnaire is complex, and physicians were recompensed for lost practice time. Data analysis was done by Stethos, specialists in market research in the field of healthcare (Stethos, Milan, Italy) in combination with University personnel. All of the physicians who took part gave their written consent, and a copy of the questionnaire is included in the supplementary materials on-line.

Results

A cross sectional comparison of the two countries' responses is shown in Table 1. As might be expected, there are both commonalities and differences between the two groups of physicians. Among the commonalities are near-identical systolic (SBP) and

diastolic (DBP) levels of blood pressure; the presenting symptoms (headache/dizziness together comprise 80% in both countries); a female (57-59%) to male (42-43%) preponderance in both groups; an identical figure for the diagnostician of resistant hypertension (specialists 54%, primary care physicians 46%); and finally an identical figure for the percentage (8%) of patients diagnosed with resistant hypertension.

Some differences between the two groups may be relevant for the diagnosis of PA, others may not. On average, German physicians were responsible for 1747 patients, their Italian counterparts for 1388. The Italians diagnosed hypertension in 18% of their patients, the Germans 25%. Both groups referred patients primarily to cardiologists (Italy 74%, Germany 59%) with lesser percentages to Departments of Medicine and specialized Hypertension Centres. The Italians were apparently much more in favour of monitoring renin and aldosterone (rating its importance on a scale from 1 to 10, 6.4/10 vs 5.4/10 in Italy and Germany, respectively), but despite this, sent only on average just over half as many (5/4/11) each year for PAC/renin/ARR measurements as their German counterparts (8/8/15). Of the Italian respondents, 36% had no patients with PA, almost double the figure for Germany (19%). On average 1% of all the Italian hypertensives were diagnosed with PA, and 2% of German (Figure 1).

At diagnosis of hypertension 50% of GPs in Italy and 43% of GPs in Germany ordered diagnostic tests. Plasma potassium levels were only requested by 43% (Italy) and 58% (Germany); renin and aldosterone measurements by 7% (Italy) and 8%(Germany) (Figure 2); of note renin and aldosterone levels were measured in only 3% of patients before starting pharmacological therapy in both countries. No GP's recognized hyperaldosteronism as a cause of resistant hypertension, or ordered renin and aldosterone measurements before changing any therapy.

Notwithstanding the numbers of tests actually requested, 8% of patients were considered potentially eligible for aldosterone and renin measurement by GPs in Italy compared to 13% of patients by GPs in Germany.

In short, there is widespread acceptance of the existence of resistant hypertension in both countries, although the common figure (8%) is low, even with false diagnosis due to compliance failure factored in. Almost half the physicians in both groups are confident to diagnose and manage resistant hypertension: there is no mention of mineralocorticoid receptor antagonists (MRAs) among the list of current therapies, and 'other' is a figure well below 8%. In contrast, recognition of PA seems to vary widely: whereas in Germany 19% of physicians have no PA patients, 11% have >20 and another 20% 10-20 such patients, for example. These latter practitioners thus have a prevalence for PA more or less in the normal range for strict cut-offs, or ~5% of hypertensives. However, the figures are overall not reflective of current best practice - ~1% of all hypertensives in Italy, and ~2% in Germany.

Discussion

The findings of the survey will be discussed under three headings. The first is a consideration of the results found from the survey. The second is an attempt to address the basis of the physicians' responses, their causes and what these causes might imply. The third is to suggest how the situation might be improved, as simply and as economically as possible.

In terms of study itself, there are a number of inevitable limitations. The data were generated by web interview. The questions are often simple, but often also requiring numeric answers: responses by web are thus likely to be 'ball-park' figures. Secondly, in both countries over 80% of patients presented with headache and /or dizziness, unremarkable given the *average* blood pressure at first visit (Italy 167/97, Germany 170/99). What are remarkable are two issues. First there appear to be no data on incidental finding of raised blood pressure, which

is common in jurisdictions where blood pressure measurement is a routine part of any but the most trivial general practice consultation. Secondly, these *average* values are very high, and in both countries presumably indicate a substantial number of subjects with even higher values. Given the documented increase in prevalence of PA progressively with increased blood pressure (1), the patient cohorts under study are likely to have levels of PA well above the average for unselected primary care patients (6) of ~5%. This makes the finding of only 1-2% even more disappointing.

There are, in addition a number of differences between the two cohorts that need to be addressed. The difference in prevalence of hypertension reported (Italy 15%, Germany 25%), taken with the equivalent values for blood pressure at time zero, is not easy to explain on the basis of genetics, epigenetics or lifestyle: a possible explanation is that there is a lower rate of consultation in Germany for reasons other than hypertension. While the percentage referral to a specialist is similar (Italy 15.2%, Germany 17.5%) , in Italy 74% of referred patients are seen by a cardiologist, while in Germany the percentage is 59%. For the patients that remain in primary care, in Germany appropriately and unsurprisingly 99.5% of patients undergo BP monitoring, compared with 78.1% in Italy. In both countries the percentage of patients who appear to have resistant hypertension is the same (8%), and in both countries this seems to be the primary focus. In both countries substantial blood pressure lowering in response to treatment was reported: however calculated, in Germany this was 20-21%, and – given clearly less aggressive pharmacotherapy – a surprising figure of 40-42% in Italy. Similarly surprising was that in a substantial minority of patients (Italy 23%, Germany 34%) hypertension was considered secondary to heart disease, rather than the converse.

In terms of the basis of the physicians' responses, their causes and what these causes might imply, there are almost certainly a variety of contributing factors. Many physicians were taught that primary aldosteronism is a rare (<1%) and relatively benign cause of secondary hypertension, both of which we now know not to be the case. As previously noted, 36% of

primary care physicians in Italy, and 19% in Germany, profess to have no case of primary aldosteronism among their hypertensive patients. The questionnaire details average patient ages, at presentation and at the time of interview: no data were presumed for physicians' age. If physicians' age data are available, it would also be of interest to look at those who have >10 and >20 patients with primary aldosteronism under their care.

Secondly, in both countries around half of the respondents knew of the guidelines, but there were no data on what percentage were actually conversant with their recommendations. Direct questions on content might have been regarded as too intrusive, but indirect questions ("At what level of presenting blood pressure is it appropriate to test for primary aldosteronism?" "What do you regard as the percentage of hypertensives whose condition is due to primary aldosteronism?") would have been useful, and added to what can only be surmised from the number of patients with primary aldosteronism in your practice question. If possible, a finer-grained analysis of those respondents with >10 or >20 primary aldosterone patients might also be illuminating – not just age, but practice location, referral patterns and so on.

Referral patterns – the major speciality relied upon being cardiology – might also underlie the low discovery rates. In Germany, when patients are referred it is to cardiologists in three fifths of cases, and in Italy three quarters. In most jurisdictions there are far more cardiologists than endocrinologists, with the latter largely occupied with diabetes, thyroid disease and reproductive issues. Although primary aldosteronism is primarily an endocrine disorder, with secondary cardiovascular and renal consequences, not all endocrinologists are practised in its management: referral for suspected primary aldosteronism should therefore be to an endocrinologist familiar with the condition, or to a specialised hypertension centre with an appropriate track record and personnel. This latter in fact should be the case for all referred patients: although clearly some cardiologists are skilled in managing hypertension, it is – as noted previously – a condition in which cardiac effects are secondary,

202 and more specialised skills – in vascular biology, clinical pharmacology, neuroscience and
203 endocrinology – are more suited to identify and rectify the root causes.

204 A fourth possible reason for under-diagnosis is that of the cost to the patient, immediate and
205 future. Ordering of tests at presentation is much more common in Italy than in Germany – for
206 example, the percentage of hypertensives undergoing ECG examination is over 10-fold
207 higher, and creatine levels over 9-fold higher – so no common attitude to testing appears to
208 exist. In fact, the costs of doing a aldosterone to renin ratio are not prohibitive, and easily
209 outweighed by the savings in appropriate management. Probably of less immediate concern
210 are the costs consequent upon confirmation of primary aldosteronism – exclusion testing,
211 imaging, lateralization, and surgery in the case of unilateral disease. As will be further
212 discussed, those are real concerns, but almost certainly a minor contributor to the very low
213 level of case detection.

214 Finally, a cause for under diagnosis may be a fear of ‘losing the patient’, particularly if
215 referral is made to an unfamiliar endocrinologist/ hypertension centre rather than a familiar
216 cardiologist colleague. There are no direct questions in the survey bearing on this: the
217 finding that over 25% of German physicians have >10 patients with primary aldosteronism
218 (10-19 15%, ≥20 11%) compared with Italy (10-19 10%, ≥20 2%) fits with the much higher
219 referral rate to cardiologists. That such patients remain in the primary care physicians
220 practice is evidence that not all referred patients are lost; what is not clear is the percentage
221 that may be. What may or may not be relevant is the u-shaped curve for the number (0, 1, 2,
222 3, 4, 5-9, 10-19, ≥20) of patients in each practice, with a nadir at 4 in both countries (Italy
223 4%, Germany 1%), a much lower figure than that for 0/1/2/3.

224 Given the findings of the survey, broad ranging but inevitably limited, how might the situation
225 be improved, as simply and as economically as possible? First might be the translation and
226 distribution of the Endocrine Society’s Guidelines’ accompanying desk reference; the cost is
227 relatively trivial, and the distribution might be accompanied by an explanatory letter from the

228 German and Italian members of the Guidelines taskforce. Secondly, in terms of cost, one of
229 the key recommendations of the 2016 guidelines needs to be highlighted, which is that if
230 patients test positive on the case detection step (determining the aldosterone to renin ratio)
231 but are unwilling or unable to proceed they should have a mineralocorticoid receptor
232 antagonist included in their antihypertensive therapy. To the extent that either cost to the
233 patient, or understandable bottlenecks in the optimal patient pathway
234 (confirmation/imaging/lateralization/unilateral adrenalectomy) make entry into the pathway
235 difficult, a low dose mineralocorticoid antagonist is an important addition. Recognition of this
236 course of action for 'low-grade' possible PA (moderate hypertension, normokalemic,
237 modestly elevated ARR, PAC in normal range) may thus encourage primary care physicians
238 to order more ARR testing in their hypertensive patients - or failing that, a simple renin
239 determination. (7,8)

240 The importance of this, what might be termed an interim strategy, is that there is increasing
241 evidence that 'inappropriate aldosterone secretion' – i.e. primary aldosteronism – might
242 contribute to elevated blood pressure in 30-50% of hypertensive patients, rather than 5-10%.
243 The first substantial study to suggest this (9) was published over 30 years ago; more
244 recently, there is clear evidence for mineralocorticoid receptor activation contributing to
245 blood pressure elevation in resistant hypertension (10), low renin hypertension (11) and
246 simple uncomplicated essential hypertension (12). In these latter cases, the ligand activating
247 mineralocorticoid receptors may not be aldosterone, but cortisol in the context of tissue
248 damage. On the other hand, recent studies from Athens suggest very strongly that the true
249 prevalence of primary aldosteronism in hypertension may be ~50%, reflecting neglect of
250 ACTH as a secretagogue (13, 14).

251 Whatever the prevalence of primary aldosteronism overall, it is likely that that of aldosterone
252 producing adenomas will remain close to its currently accepted levels, i.e. 3-4% of
253 hypertensives. Patients with APA commonly have more florid disease (higher PAC, ARR,
254 blood pressure and incidence of hypokalemia), and are thus more easily ascertained.

255 Unfortunately the questionnaire did not address the outcomes of diagnosis of primary
256 aldosteronism in either country – whether most or all so diagnosed were patients with
257 aldosterone producing adenoma.

258 Primary aldosteronism is a rapidly moving field, and the advances of the past couple of
259 decades are obviously yet to be appreciated and acted upon by the profession. To the effect
260 that they have been, primary care physicians today may be discouraged in terms of
261 screening, let alone committing a patient to an agreed pathway of ideal treatment, for
262 reasons of cost: capacity limitations, particularly of interventionists skilled in adrenal venous
263 sampling, are an additional stumbling block. Over the next decade (perhaps even the next
264 five years) appreciation of the role of mineralocorticoid receptor activation – by
265 inappropriately high aldosterone levels, or by normal levels of cortisol in the context of tissue
266 damage – may begin to increase the use of inexpensive, low dose minimal side-effect
267 mineralocorticoid receptor antagonists as part of first line therapy in hypertension.

268

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Figure Legends

Figure 1. Prevalence of primary aldosteronism, other forms of secondary hypertension and essential hypertension in Italy and Germany.

Figure 2. Proportion of patients screened for PA or not, and with a final diagnosis of PA, in Italy and Germany.

Questionnaire for GPs	Italy	Germany
Number of patients seen by each GP (mean)	1388	1747
Prevalence of HTN (%)	18	25
SBP/DBP on diagnosis of HTN (mean, mmHg)	167/97	170/99
Prevalence of resistant HTN (%)	7.6	7.9
Patients ordered tests on diagnosis of HTN (%)	50	43
Plasma [K ⁺] measured on diagnosis of HTN (%)	43	58
Aldosterone and renin measurement on diagnosis of HTN (%)	7	8
Aldosterone and renin measurement before drug therapy (%)	3	3
Awareness of the ES guidelines for PA (%)	53	59
Patients tested last year for aldosterone alone/renin alone/both	5/4/11	8/8/15
GPs reporting no patients with PA (%)	36	19
Overall reported PA prevalence in HTN (%)	1	2

Table 1. Relevant questions and replies on PA awareness by Italian and German general practitioners.

GPs= general practitioners; PA= primary aldosteronism; HTN= hypertension; ES= Endocrine Society.

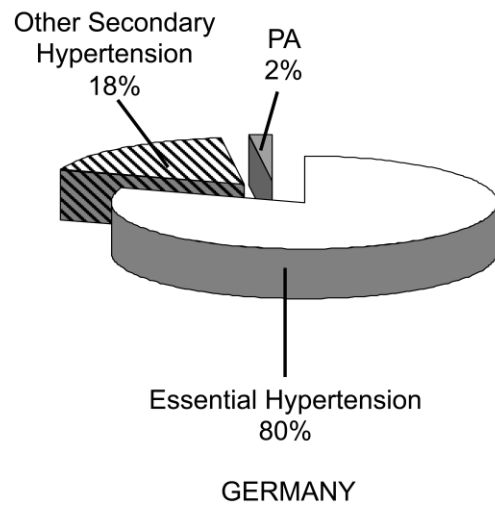
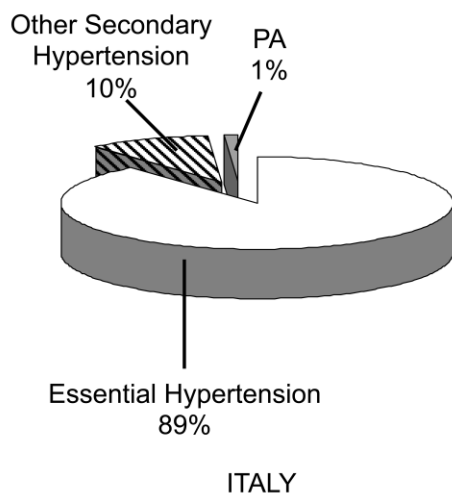


Figure 1

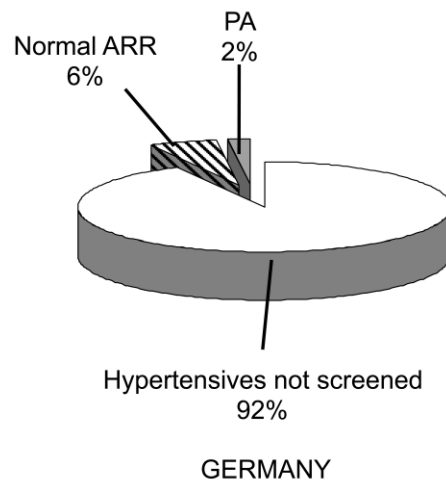
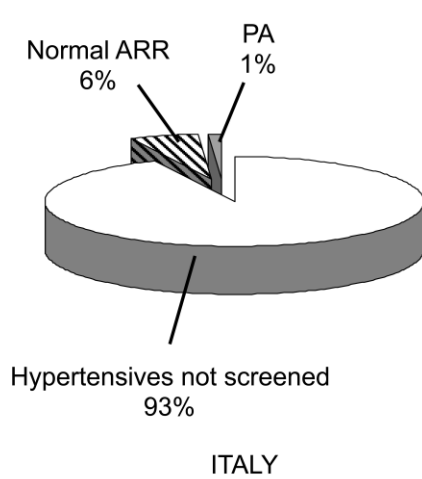


Figure 2